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Thyroid Cancer After Radiotherapy for Childhood Cancer

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Abstract. The thyroid gland in children is among the most sensitive organs to the carcinogenic effects of ionizing radiation, and very young children are at especially high risk. Risk associated with exposure to external X- or γ-radiation increases linearly with increasing dose to the thyroid gland at low-to-moderate doses, but the dose–response relationship appears to flatten at the very high doses characteristic of cancer radiotherapy. Because of the extreme sensitivity of the thyroid gland in children, there is a risk of radiation-induced thyroid cancer even when the thyroid gland is outside of the irradiated field. Increased incidence of thyroid cancer has been noted following radiotherapy for childhood Hodgkin disease, non-Hodgkin lymphoma, neuroblastoma, Wilms tumor, acute lymphocytic leukemia and tumors of the central nervous system. Radiation-induced tumors begin to appear 5–10 years after irradiation and excess risk persists for decades, perhaps for the remainder of life. The background incidence of thyroid cancer is two- to threefold higher among females than males, and the absolute increase in risk due to irradiation is higher in females as well. Most of the thyroid cancers that occur in association with irradiation are of the papillary type, for which the cure rate is high if tumors are detected early. This highlights the importance of long-term surveillance of persons irradiated during childhood. Important areas for research include the possibility that children with certain types of first cancer are especially susceptible, the basis of the greater female susceptibility, the joint effects of radiation and other factors, and genetic mechanisms in radiation-induced and spontaneously occurring thyroid cancer. Med. Pediatr. Oncol. 36:568–573, 2001. © 2001 Wiley-Liss, Inc.

Key words: thyroid neoplasms; radiotherapy; second cancers; epidemiologic studies

INTRODUCTION

The thyroid gland in children is well known to be among the most sensitive organs to the carcinogenic effects of ionizing radiation [1], so it is not surprising that thyroid cancer is among the more common radiotherapy-induced second cancers among survivors of childhood cancer [2]. Excess thyroid cancer has been reported following radiotherapy for childhood Hodgkin disease, non-Hodgkin lymphoma, neuroblastoma, Wilms tumor, acute lymphocytic leukemia and tumors of the central nervous system [2–6]. Fortunately, it is also among the most curable of cancers [7], and very few childhood cancer survivors die of a radiation-induced thyroid cancer. Mortality risks associated with a possible second thyroid cancer pale in comparison with those associated with the first primary cancer and other possible treatment induced second cancers, such as breast, brain, lung or bone, or leukemia. Nonetheless, 5–10% of thyroid cancers are fatal [7]. Although concern with secondary thyroid cancer is not a paramount consideration in the management of childhood cancer patients, it is an important one, and an understanding of who is at highest risk can help to guide post-treatment surveillance.

The primary objectives for this brief review are to identify important predictors of risk of secondary thyroid cancer among persons with a history of radiotherapy (RT) for a childhood cancer and to consider the likely magnitude of risks attributable to radiation. Because current understanding of radiation-induced thyroid cancer is based, in large part, on studies of persons irradiated for benign conditions during childhood and survivors of the atomic bomb explosions in Japan [8–13], I will draw on those studies here, as well as on studies of second cancers [3,6]. The risk of thyroid cancer associated with exposure to radioiodines, such as from medical procedures or nuclear reactor accidents, is an important issue for radiation thyroid carcinogenesis in general [14,15], but not in the context of secondary thyroid cancer following childhood cancer, and is not addressed here.

HISTORICAL

Early clues to the etiologic importance of ionizing radiation in thyroid carcinogenesis came from descriptions of series of cases of thyroid cancer in children and

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adolescents, which noted high frequencies of histories of radiotherapy to the head and neck earlier in childhood [16–20]. These reports of case series motivated large epidemiologic studies, which confirmed the clinical impressions, provided quantitative information on the level of risk associated with a given dose of radiation to the thyroid gland, described the pattern of excess risk over time, and identified subgroups of the population that were particularly susceptible [e.g. 8–11,21].

In the early thyroid cancer case series, the radiotherapy was given more often for any of a variety of benign conditions of the head or neck than for a first malignancy. Such treatments were very common in the United States between 1920 and 1960 [22,23], and long-term survival of patients irradiated for benign conditions was not seriously compromised by their baseline illness. On the other hand, long-term survival of childhood cancer patients was unusual, and radiation-induced second cancers were uncommon. Childhood radiotherapy for benign disease is believed to be an important contributor to the increased incidence of thyroid cancer in the United States between the 1930s and 1970s [24–26]. The use of radiation to treat benign conditions of the head and neck was largely discontinued by 1960, and such exposures have receded as important causes of thyroid cancers occurring today. On the other hand, radiation continues to be widely used in the treatment of childhood cancer, and approximately 70% of childhood cancer patients now can be cured through aggressive therapy [27]. In the future, most radiotherapy-induced thyroid cancers will occur among cancer survivors.

SPONTANEOUS AND RADIATION-INDUCED THYROID CANCER

Thyroid cancer occurs in a variety of forms, ranging from well-differentiated and highly curable papillary and follicular carcinomas to poorly differentiated and rapidly fatal anaplastic carcinoma [28] (Table I). Fortunately, papillary carcinoma, the type with the most favorable prognosis, is also the most common, and anaplastic carcinoma is the least common. Papillary carcinoma accounts for approximately 60% of cases, follicular carcinomas for another 20%, and medullary and anaplastic carcinoma for 5–15%, but these percentages vary depending on the age composition and geographic location of the population [15]. Papillary and follicular carcinomas both arise from follicle cells (unlike medullary cancer, which arises from parafollicular C cells), but they behave very differently clinically, exhibit different epidemiologic associations, and appear to develop through different genetic pathways [28–32].

TABLE I. Principal Types of Thyroid Cancer (Based on Ron [15])

Type[a]	Percent	Radiation-induced?	Survival
Papillary	60	+ + +	Very good
Follicular	20	+	Intermediate
Medullary	5-15	−	Intermediate
Anaplastic	5-15	−/?	Very poor

[a]Other, uncommon types of thyroid cancer include lymphoma and sarcoma.

Papillary carcinoma is the type of thyroid cancer usually observed to occur in excess following radiation exposure and often accounts for 75–90% of thyroid cancers following high dose, childhood exposures [1,3,6,13]. Follicular cancers are also caused by radiation, though less often, and medullary cancers have not been associated with radiation [1]. Few irradiated populations have been followed through the range of ages when anaplastic carcinoma tends to occur, and it would be premature to conclude that this uncommon, but deadly, form of thyroid cancer cannot be caused by radiation. A small fraction of RT-induced papillary or follicular tumors might evolve into an anaplastic cancer. Follicular cancer also occurs at an older age, on average, than papillary cancer, and longer follow-up may reveal a stronger association between radiation and this subtype than has been observed to date.

The background incidence rate of papillary thyroid cancer increases with increasing age during young- and middle-age, but then declines [33]. Incidence, is higher among females than males, particularly at younger ages. The female-to-male incidence ratio decreases from approximately 5 for persons younger than 30 years to about 1.5 for those older than 60 years [7]. An important issue is whether the effect of radiation exposure is to *add* to the baseline risk or to *multiply* it. The two possibilities imply very different patterns of absolute excess risk over time and between the sexes.

DETERMINANTS OF RISK OF RADIOGENIC THYROID CANCER

Radiation Dose

Pooled analysis of results from studies of atomic bomb survivors and populations irradiated for benign diseases of the head and neck suggests that risk increases linearly with increasing dose over a broad range of doses to the thyroid gland, with increases seen at doses as low as 0.1 Gy [13]. The shape of the dose-response at high doses, such as those associated with cancer radiotherapy, is not well-defined, as sample sizes are small, but results suggest a flattening of the dose-response relationship at doses greater than approximately 5 Gy [3,6] (Fig. 1). Such a flattening of the dose-response could be explained by a balance between cytotoxic and carcinogenic effects of ionizing radiation [3]. Very high radiation doses can block cells' ability to proliferate, and a cell that cannot proliferate cannot give rise to a malignant clone. That high radiation doses can kill, or inactivate, follicular cells

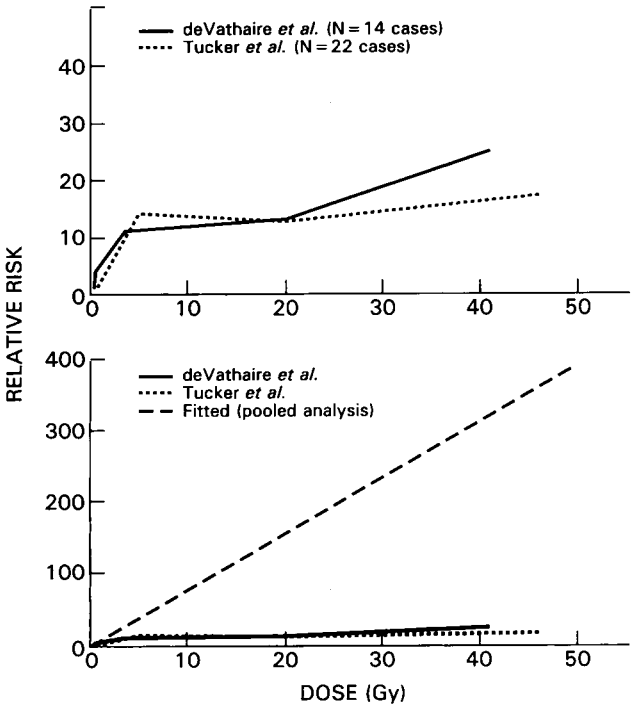

Fig. 1. Relative risk of thyroid cancer by radiation dose to the thyroid gland among childhood cancer survivors. **Upper panel** shows data from the second cancer studies of Tucker et al. [3] and de Vathaire et al. [6]. Reference category for Tucker et al. was dose less than 2 Gy; relative risks likely would have been substantially higher if a true nonexposed group had been used. **Lower panel** shows the same curves as in the upper panel plotted on a different scale for relative risk and also including a linear extrapolation of a fitted dose-response for populations primarily exposed to much lower doses, based on results of Ron et al. [13].

is indicated by the observation that cancer radiotherapy often causes at least temporary hypothyroidism [23,34]. (The reference category for the analysis of Tucker et al. [3] was dose <2 Gy, rather than 0 Gy. This influences the magnitude of the relative risk estimates for higher doses, but not the shape of the dose-response relationship.)

Based largely on populations exposed to low-to-moderate doses, the absolute risk was estimated to increase by 4–5 cases per 10,000 persons per year, for each Gy of radiation dose to the thyroid gland, and the relative risk by 7.7 per Gy [13]. Among childhood cancer survivors, the average excess absolute risk probably is closer to 0.4 cases per 10^4 PY-Gy, and the excess RR per Gy closer to 1.1 per Gy [3,13,14]. This would imply an expectation of approximately 200 radiogenic thyroid cancers among 10,000 children who received thyroid doses of 20 Gy and were followed for 25 years.

The limited available data concerning the effects of dose fractionation suggest that fractionation lessens the risk relative to acute exposure, but not dramatically [13].

TABLE II. Excess Relative Risk (RR) of Thyroid Cancer by Age at Time of Irradiation Among Atomic Bomb Survivors (Modified After Thompson et al. [12])

	Excess RR (per Gy)	
Age at Exposure (years)	Females	Males
0–9	9.5	9.4
10–19	3.1	2.6
20–39	0.4	−0.2
≥ 40	−0.2	−0.2

Age at Time of Irradiation

Age at the time of irradiation is as good, if not better, an indicator of the risk of radiation-induced thyroid cancer as radiation dose [35,36], particularly in the context of radiotherapy for pediatric cancer. Studies of the atomic bomb survivors, one of the few populations for which it is possible to assess radiation risks over a wide range of ages at exposure, show a striking decrease in radiation risk estimates with increasing age at exposure (Table II) [12]. In this population, there is no evidence of radiogenic thyroid cancer among persons who were older than 20–39 years at the time the bombs were dropped. Similarly, the risk of radiogenic thyroid cancer was higher among children and adolescents treated for Hodgkin disease than it was for adults [3,37,38]. An inverse association between susceptibility and age at exposure is apparent even among children, and children younger than 5 years are particularly sensitive [8,39].

The inverse association between age at irradiation and thyroid cancer risk probably reflects age-related changes in cell proliferation within the thyroid gland [40]. Potentially mutagenic exposures to actively dividing cells, or cells with an active growth phase still ahead of them, may carry greater risk than when the cells have completed their growth phase [40].

Time Since Irradiation

Thyroid cancers caused by exposure to external X- or γ-radiation typically begin to appear about 5–10 years after exposure [1,13,14]. The relative excess typically reaches a maximum between 10 and 20 years after exposure and then declines, whereas the absolute excess remains elevated [13,14]. Excess risk is still apparent in populations after 30–50 years [13,14] and may well persist for life. There is no evidence of a window of time after which a person irradiated in childhood can be assumed to have the same risk as a nonirradiated person of the same age and sex. Radiogenic thyroid cancers typically do not appear until after children have reached puberty [1,16]. The interval between exposure and diagnosis of a thyroid cancer is influenced by the level

of medical surveillance. Screening of asymptomatic persons will, of course, lead to earlier diagnosis.

Sex

The incidence rate of thyroid cancer is approximately three times as high in females as in males [7,33]. If a given dose of radiation increases the risk of thyroid cancer by the same *relative* amount in males and females, this would imply a threefold greater *absolute* risk associated with radiotherapy in females. Although different patterns have been observed in different populations, the balance of the evidence is consistent with the view that the absolute risk is indeed higher in females [1,13].

Type of First Cancer

The risk of radiation-induced, secondary thyroid cancer would be expected to vary among different types of childhood cancer based on differences in average age at diagnosis and degree of thyroid exposure alone. For example, neuroblastoma and Wilms tumor, which tend to occur at younger ages than other types of childhood cancer, were associated with higher absolute risks (per Gy) of radiation-induced thyroid cancer than either Hodgkin disease or non-Hodgkin lymphoma (NHL) [3] (Table III). It is possible that cell-killing associated with the higher thyroid doses from lymphoma treatments also contributed to these differences.

Whether the type of first childhood cancer might serve as a marker of susceptibility to radiogenic or spontaneous thyroid cancer beyond any difference that can be explained by dose or age at diagnosis (irradiation), is not clear. Such shared susceptibility might arise if thyroid cancer and a particular type of childhood cancer have genetic or environmental causes in common [41]. In one study of childhood cancer survivors, dose-response analysis for secondary thyroid cancer indicated a higher risk of thyroid cancer for any given thyroid dose among persons with a first neuroblastoma than in persons with a first cancer of another type (Table IV) [6,41,42]. However, this finding has not been replicated [43], so a degree of caution in interpretation is warranted. The analysis of deVathaire et al. [6] took age at diagnosis of the first cancer into account, but lack of overlap in the age at exposure and thyroid dose distributions for different types of first cancer can make it difficult to dissociate the effects of dose, age at exposure, and other determinants of susceptibility.

TABLE IV. Relative Risk (RR) of Second Thyroid Cancer, by Type of First Childhood Cancer and Radiation Dose to the Thyroid Gland (From deVathaire et al. [6])

	RR[a] (no. cases) dose to thyroid gland (Gy)	
Type of first cancer	<5	>5
Neuroblastoma	160 (3)	1,532 (2)
Other type	11 (2)	157 (7)

[a]Standardized incidence ratio, based on general population comparison.

Other Factors

The thyroid gland is under the feedback control of the hypothalamus and anterior pituitary gland, and disruption of this axis due to any of a variety of endogenous or exogenous causes might influence the risk of thyroid tumors [44]. If serum levels of the thyroid hormones triiodothyronine (T3) and thyroxine (T4) drop too low, the hypothalamus signals the pituitary to release thyroid stimulating hormone (TSH), which stimulates proliferation of follicular cells in the thyroid gland. Any factor that contributes to low blood levels of thyroid hormones, such as iodide deficiency or goitrogens in the diet, or otherwise leads to the release of TSH from the pituitary, can stimulate cell division in the thyroid gland. Such stimulation could potentiate effects of irradiation by leading to the expression of radiation-induced DNA damage that would otherwise remain quiescent [40]. However, iodine deficiency and goitrogens have been linked more closely with increased incidence of follicular carcinoma than papillary carcinoma [15,29], whereas papillary cancer is the type most strongly linked to radiation.

The female predominance of thyroid cancer points to a likely role for hormonal or other reproductive factors. Whether such factors might also modify risks associated with exposure to radiation is unclear [14]. The study of interaction typically requires large sample sizes.

TABLE III. Absolute Excess Risk of Radiotherapy-Induced Thyroid Cancer by Type of First Childhood Cancer (Modified After Tucker et al. [3])

Type of first cancer	Number of patients	Mean age at diagnosis (years)[a]	Thyroid dose (Gy)	Thyroid cancers	Excess risk (per 10^4 PY-Gy)
Neuroblastoma	790	2	6.6	7	2.1
Wilms Tumor	1,248	3	3.1	4	1.6
Hodgkin disease	1,036	11	31.0	5	0.3
non-Hodgkin lymphoma	422	9	24.0	2	0.3

[a]Age at diagnosis of first cancer.

To date, neither alkylating agents nor other cytotoxic drugs have been implicated in the occurrence of secondary thyroid cancers, and there is little or no evidence of synergistic effects of chemotherapy with radiotherapy.

INFLUENCE OF SCREENING

The apparent incidence of thyroid cancer is influenced by the aggressiveness of case-finding. Papillary thyroid cancer often is asymptomatic, and the probability and timing of detection of ''occult'' tumors depends on the level of medical surveillance [12,13,45]. This may contribute to the very large relative risks for thyroid cancer reported when cancer patients or other irradiated populations under close medical surveillance are contrasted with the experience of a general population not subjected to equally close diagnostic effort.

The realization that people given head or neck radiotherapy during childhood were at increased risk of thyroid cancer led to large-scale thyroid screening of asymptomatic populations known to have a history of radiotherapy to the neck region [45]. This screening identified large numbers of occult thyroid tumors [45]. The apparent *absolute* risk due to radiotherapy was higher in a screened population than in an unscreened population [13]. However, the slope of the relationship between the excess *relative* risk of thyroid cancer and radiation dose was similar before and after the screening, which suggests that radiation causes both clinical and subclinical, thyroid tumors [10]. Similarly, twofold higher incidence rates of thyroid cancer were observed among atomic bomb survivors who came to a clinic for free, biannual physical examinations than for those who did not participate in this program [12,13].

The proper clinical management of asymptomatic patients found to have small thyroid tumors or nodules has long been a controversial issue [46,47]. At a minimum, such patients need to be followed closely [23,47]. There is little evidence that radiation-induced papillary thyroid cancers behave differently clinically than spontaneous tumors [22,47].

CHANGES IN RADIOTHERAPY FOR PEDIATRIC CANCER

Clinical trials have demonstrated that treatment outcomes for many childhood cancers are not compromised by the use of lower-dose radiotherapy regimens, or even by the exclusion of radiotherapy altogether [48–50]. This, together with appreciation of the adverse long-term side effects of radiotherapy during childhood, has led to the curtailment or elimination of radiotherapy in many instances, including that for Hodgkin disease, non-Hodgkin lymphoma, acute lymphocytic leukemia, and Wilms tumor. Current practice less often involves high radiation doses given in large fractions to extended fields, and cranial radiotherapy often is deferred, if possible, until children are at least 3 years old [48,50]. One would expect the risk of secondary thyroid cancer associated with current treatments to be somewhat lower than for treatments of previous decades. However, children irradiated under earlier treatment regimens will remain at risk of second cancer for years to come.

SUMMARY

Secondary thyroid cancer is an important, but manageable, delayed effect of radiotherapy for childhood cancer. The usual type of radiation-induced thyroid cancer is papillary carcinoma, and such tumors do not appear to differ clinically from spontaneously occurring papillary cancers diagnosed at the same age. If detected early, most cases can be cured, and mortality risks are low compared to those associated with an ineffectively treated primary cancer. The risk of thyroid cancer increases with increasing radiation dose, but at a decelerating rate for doses in excess of approximately 5 Gy. Risk appears to be less sensitive to variation in dose at high doses, and age at irradiation for the first cancer may be a stronger determinant of risk. Infants and young children are at especially high risk of radiogenic thyroid cancer, and females are at higher risk than males. The excess risk typically first appears 5–10 years after radiotherapy and, for clinical purposes, should be assumed to persist for the remainder of life among persons with intact thyroid glands. Whether patients with certain types of childhood cancer are at particularly high risk of secondary, radiation-induced thyroid cancer, beyond that explainable in terms of age, sex or radiation dose, is an open question. With ongoing advances in research into the roles of specific oncogenes and growth factors in thyroid carcinogenesis, prospects appear favorable for improved understanding of the mechanistic basis of these epidemiologic associations.

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